In the Claims

Please amend claims 3-8, 10-43 and 45-46 as set forth below.

Please cancel claim 44 without prejudice.

Please add new claim 47 as presented below.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. (Original) A crystal comprising a pRb/$E2F_{(409-426)}$ complex, wherein the crystal structure is characterised by the atomic co-ordinates of Annex 1.

2. (Original) A crystal as claimed in claim 1, wherein the interactions between $E2F_{(409-426)}$ and pRb comprise one or more of the following interactions:

$E2F_{(409-426)}$ residue	**pRb residue**
Leu_{409}	Lys_{548}
Tyr_{411}	Glu_{551}
Tyr_{411}	Ile_{532}
Tyr_{411}	Glu_{554}
His_{412}	Arg_{656}
His_{412}	Lys_{653}
Gly_{414}	Glu_{533}
Gly_{414}	Lys_{652}
Leu_{415}	Leu_{649}
Leu_{415}	Glu_{553}
Leu_{415}	Lys_{537}
Glu_{417}	Lys_{537}
Gly_{418}	Arg_{467}
Glu_{419}	Thr_{645}

Arg_{422}	Glu_{464}
Asp_{423}	Arg_{467}
Leu_{424}	Lys_{530}
Phe_{425}	Phe_{482}
Phe_{425}	Lys_{475}

3. (Currently Amended) A method ~~to identify~~ of identifying an agent which modulates the interaction between pRb and $E2F_{(409-426)}$, ~~the method~~ comprising:
   a) combining ~~together~~ pRb, $E2F_{(409-426)}$ and an agent, under conditions in which pRb and $E2F_{(409-426)}$ form a complex;
   b) growing a crystal structure of any pRb/ $E2F_{(409-426)}$ complex; and
   c) ~~analysing~~ analyzing the crystal to determine whether the agent ~~is an agent which~~ modulates the interaction between pRb and $E2F_{(409-426)}$.

4. (Currently Amended) [[A]] The method[[,]] ~~as claimed in~~ of claim 3, wherein ~~the combining of the components is~~ pRb is combined with the agent and ~~then~~ $E2F_{(409-426)}$ is subsequently added.

5. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 3, wherein ~~the combining of the components is~~ $E2F_{(409-426)}$ is combined with the agent and ~~then~~ pRb is subsequently added.

6. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 3, wherein ~~the combining of the components is~~ pRb is combined with $E2F_{(409-426)}$ and ~~then~~ the agent is subsequently added.

7. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 3 ~~to 6,~~ wherein step c) comprises comparing the crystal structure to the crystal structure ~~of claim 1~~ characterized by the atomic co-ordinates of Annex 1.

8. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 3 ~~to 7~~, wherein the agent is selected using the three dimensional atomic co-ordinates of Annex 1.

9. (Original) A method of identifying an agent that modulates a pRb/$E2F_{(409-426)}$ complex, comprising selecting an agent using the three-dimensional atomic coordinates of Annex 1.

10. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 9, wherein said ~~selection~~ selecting is performed in conjunction with computer modeling.

11. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 9 ~~or 10~~, ~~wherein the method~~ further ~~comprises~~ comprising the steps of:

a) contacting the selected agent with pRb and $E2F_{(409-426)}$ under conditions in which pRb and $E2F_{(409-426)}$ can form a complex; and

b) measuring the binding affinity of pRb to $E2F_{(409-426)}$ in the presence of the agent and comparing the binding affinity to that of pRb to $E2F_{(409-426)}$ when in the absence of the agent, wherein an agent modulates a pRb/$E2F_{(409-426)}$ complex when there is a change in the binding affinity of pRb to $E2F_{(409-426)}$ when in the presence of the agent.

12. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 11, ~~wherein the method~~ further comprising:

a) growing a supplementary crystal from a solution containing pRb and $E2F_{(409-426)}$ and the selected agent where said agent changes the binding affinity of the pRb/$E2F_{(409-426)}$ complex under conditions in which pRb and $E2F_{(409-426)}$ can form a complex;

b) determining the three-dimensional atomic coordinates of the supplementary crystal by X-ray diffraction using molecular replacement analysis;

c) comparing the three dimensional coordinates with those for the crystal structure as ~~claimed in claim 1~~ characterized by the atomic co-ordinates of Annex 1; and

d) selecting a second generation agent using the three-dimensional atomic coordinates determined for the supplementary crystal.

13. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 12, wherein said ~~selection~~ selecting is performed in conjunction with computer modeling.

14. (Currently Amended) A method of identifying an agent that modulates a pRb/$E2F_{(409-426)}$ complex, comprising:

a) contacting ~~a selected~~ an agent with pRb and $E2F_{(409-426)}$ under conditions in which pRb and $E2F_{(409-426)}$ can form a complex; and

b) measuring the binding affinity of pRb to $E2F_{(409-426)}$ in the presence of the agent and comparing the binding affinity to that of pRb to $E2F_{(409-426)}$ when in the absence of the agent, wherein an agent modulates a pRb/$E2F_{(409-426)}$ complex when there is a change in the binding affinity of pRb to $E2F_{(409-426)}$ when in the presence of the agent.

15. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 14, ~~wherein the method~~ further comprising:

a) growing a supplementary crystal from a solution containing pRb and $E2F_{(409-426)}$ and the ~~selected~~ agent wherein said agent changes the binding affinity of the pRb/$E2F_{(409-426)}$ complex under conditions in which pRb and $E2F_{(409-426)}$ can form a complex;

b) determining the three-dimensional atomic coordinates of the supplementary crystal by X-ray diffraction using molecular replacement analysis;

c) comparing the three dimensional coordinates with those for the crystal structure ~~claimed in claim 1~~ characterized by the atomic co-ordinates of Annex 1; and

d) selecting a second generation agent using the three-dimensional atomic coordinates determined for the supplementary crystal.

16. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 15, wherein said ~~selection~~ selecting is performed in conjunction with computer modeling.

17. (Currently Amended) A method of identifying an agent that modulates a pRb/$E2F_{(409-426)}$ complex, comprising:

~~a) selecting an agent;~~

[[b]]a) co-crystalising pRb with ~~the~~ an agent;

[[c]]b) determining the three dimensional coordinates of the pRb-agent association by X-ray diffraction using molecular replacement analysis; and

[[d]]c) comparing the three dimensional coordinates with those of the crystal structure claimed in claim 1.

18. (Currently Amended) A method of identifying an agent that modulates a pRb/$E2F_{(409-426)}$ complex, comprising:

~~a) selecting an agent;~~

[[b]]a) crystalising pRb and soaking ~~the~~ an agent into the crystal;

[[c]]b) determining the three dimensional coordinates of the pRb-agent association by X-ray diffraction using molecular replacement analysis; and

[[d]]c) comparing the three dimensional coordinates with those of the crystal structure claimed in claim 1.

19. (Currently Amended) A method of identifying an agent that modulates a pRb/$E2F_{(409-426)}$ complex, comprising:

~~a) selecting an agent;~~

[[b]]a) co-crystalising pRb, $E2F_{(409-426)}$ and ~~the~~ an agent;

[[c]]b) determining the three dimensional coordinates of the pRb-E2F-agent association by X-ray diffraction using molecular replacement analysis; and

[[d]]c) comparing the three dimensional coordinates with those of the crystal structure claimed in claim 1.

20. (Currently Amended) A method of identifying an agent that modulates a pRb/$E2F_{(409-426)}$ complex, comprising:

~~a) selecting an agent;~~

[[b]]a) co-crystalising pRb and $E2F_{(409-426)}$ and soaking ~~the~~ an agent into the crystal;

[[c]]b) determining the three dimensional coordinates of the pRb-E2F-agent association by X-ray diffraction using molecular replacement analysis; and

[[d]]c) comparing the three dimensional coordinates with those of the crystal structure claimed in claim 1.

21. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 17 ~~to 20~~, wherein the agent is selected using the three dimensional atomic co-ordinates of Annex 1.

22. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 17 ~~to 21~~, ~~wherein the methods~~ further ~~comprise~~ comprising selecting a second generation agent using the three dimensional atomic coordinates determined in step [[c]]b).

23. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 22, wherein the second generation agent is selected using the three dimensional atomic coordinates of Annex 1.

24. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 22 ~~or 23~~, wherein the ~~selection~~ selecting is performed in conjunction with computer modeling.

25. (Currently Amended) [[A]] The method of ~~identifying an agent as claimed in any one of~~ claim[[s]] 3 ~~to 24~~, wherein the ~~selected~~ identified agent ~~and/or the second generation agent~~ mimics a structural feature of $E2F_{(409\text{-}426)}$, when said $E2F_{(409\text{-}426)}$ is bound to pRb.

26. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 9 ~~or 10~~, ~~wherein method comprises the~~ further comprising the steps of:

a) contacting the ~~selected~~ agent with a $pRb/E2F_{(409\text{-}426)}$ complex; and

b) determining whether the agent affects the stability of the complex.

27. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 26, wherein the ~~determination~~ determining is with fluorescence polarization.

28. (Currently Amended) A method of identifying an agent that modulates a pRb/$E2F_{(409-426)}$ complex, comprising:

a) contacting a fluorescently tagged $E2F_{(409-426)}$ peptide (E2F-fluoropeptide) with pRb to allow pRb/E2F-fluoropeptide complex formation;

b) detecting the fluorescence polarization;

c) adding ~~a selected~~ an agent; and

d) detecting the fluorescence polarization in the presence of the agent.

29. (Currently Amended) A method of identifying an agent that modulates a pRb/$E2F_{(409-426)}$ complex, comprising;

a) contacting a fluorescently tagged $E2F_{(409-426)}$ peptide (E2F-fluoropeptide) with pRb to allow pRb/E2F-fluoropeptide complex formation;

b) detecting the fluorescence polarization;

c) contacting ~~a selected~~ an agent with pRb and $E2F_{(409-426)}$ peptide (E2F-fluoropeptide) under conditions in which pRb and E2F-fluoropeptide can form a complex;

d) detecting the fluorescence polarization; and

e) comparing the fluorescence polarization detected in b) and d).

30. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 28 ~~or 29~~, wherein the fluorescently tagged E2F peptide is selected using the three dimensional atomic co-ordinates of Annex 1.

31. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 28 ~~to 30~~, wherein a decrease in fluorescence polarization in the presence of the agent indicates that the agent destabilises the complex.

32. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 28 ~~to 31~~, ~~wherein the method comprises the~~ further comprising the step of adding untagged $E2F_{(409-426)}$ and detecting fluorescence polarization.

33. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 32, wherein ~~if~~ a decrease in fluorescence polarization ~~decreases,~~ upon addition of the untagged $E2F_{(409-426)}$ [[,]] is indicative that the agent does not stabilise the complex.

34. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 32 ~~or 33~~, wherein ~~if there is~~ no substantial change in fluorescence polarization[[,]] upon addition of the untagged $E2F_{(409-426)}$ [[,]] is indicative that the agent stabilises the complex.

35. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 28 ~~to 34~~, ~~wherein the method~~ further ~~comprises~~ comprising:

a) contacting a fluorescently tagged E7 peptide (E7-fluoropeptide) with pRb to allow pRb/E7-fluoropeptide complex formation;

b) detecting the fluorescence polarization;

c) adding an agent that modulates pRb/$E2F_{(409-426)}$ complex; and

d) detecting the fluorescence polarization in the presence of the agent.

36. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 28 ~~to 34~~, ~~wherein the method~~ further ~~comprises~~ comprising:

a) contacting a fluorescently tagged E7 peptide (E7-fluoropeptide) with pRb to allow pRb/E7-fluoropeptide complex formation;

b) detecting the fluorescence polarization;

c) contacting an agent that modulates pRb/$E2F_{(409-426)}$ complex with pRb and E7-fluoropeptide under conditions in which pRb and E7-fluoropeptide can from a complex;

d) detecting the fluorescence polarization; and

e) comparing the fluorescence polarization detected in b) and d).

37. (Currently Amended) [[A]] The method ~~as claimed in~~ of claim 35 ~~or 36~~, wherein a decrease in fluorescence polarization indicates that the agent also inhibits E7 binding to pRb.

38. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 11 ~~to 16~~, wherein the binding affinity is measured by isothermal titration calorimetry.

39. (Currently Amended) [[A]] The method ~~as claimed in any one~~ of claim[[s]] 11 ~~to 16~~, wherein the binding affinity is measured by Surface Plasmon Resonance (SPR).

40. (Currently Amended) ~~An agent, that modulates~~ A method of modulating the interaction between pRb and $E2F_{(409-426)}$ comprising[[,]] contacting an agent identified by [[a]] the method ~~as claimed in any one~~ of claim[[s]] 3 ~~to 39~~ with pRb and $E2F_{(409-426)}$ under conditions in which pRb and $E2F_{(409-426)}$ form a complex.

41. (Currently Amended) ~~An agent, as claimed in claim 40, for use as an apoptosis promoting factor in~~ A method for the prevention or treatment of proliferative diseases comprising contacting a cell with an agent identified by the method as claimed in claim 3, wherein the agent is an apoptosis promoting factor.

42. (Currently Amended) ~~An agent as claimed in claim 40 or 41, wherein the agent is for use in~~ A method for preventing or treating cancer, comprising contacting a cancer cell with an agent identified by the method as claimed in claim 3~~which may be pancreatic cancer and related diseases~~.

43. (Currently Amended) ~~The use of an agent,~~ A pharmaceutical composition comprising an agent which modulates the formation of a pRb/E2F$_{(409-426)}$ complex[[,]] as identified by [[a]] the method ~~as claimed in any one~~ of claims 3 ~~to 39, in the manufacture of a medicament for the prevention or treatment of proliferative diseases~~.

44. (Canceled)

45. (Currently Amended) The method of claim 40, wherein the agent is identified by use of the atomic co-ordinates of Annex 1 ~~the crystal structure as claimed in claim 1 or 2, for identifying an agent that modulates the formation of a pRb/E2F$_{(409-426)}$ complex~~.

46. (Original) Computer readable media comprising a data storage material encoded with computer readable data, wherein said computer readable data comprises a set of atomic co-ordinates of the pRb/E2F$_{(409-426)}$ crystal structure of Annex 1 recorded thereon.

47. (New) The method of claim 42, wherein the cancer is pancreatic cancer.